DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

950884

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

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**Warning Letter**

Niel T. Constantine, Ph.D.
University of Maryland School of Medicine
Institute of Human Virology
725 West Lombard Street, Room 407
Baltimore, Maryland 21201

Dear Dr. Constantine:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from July 12 to July 21, 2004. FDA investigator Stephanie Shapley met with you to review your conduct as a clinical investigator testing investigational devices in three studies. Those studies all fall under the general title, [redacted] and have the following individual protocol names:

1. Protocol [redacted] involving a Known HIV-1 positive population (hereinafter referred to as "Study 1");
2. Protocol [redacted] involving a Low Risk population (hereinafter referred to as "Study 2"); and
3. Protocol [redacted] involving a High Risk population (hereinafter referred to as "Study 3").

Testing for Studies 1 and 2 was conducted at the University of Maryland School of Medicine's Institute of Human Virology (IHV), and testing for Study 3 was conducted at the [redacted]. FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational devices.

The FDA investigator issued and discussed with you the Form FDA 483, Inspectional Observations, at the end of the inspection. We reviewed the inspection reports, the Form FDA 483, and your letter in response to the Inspectional Observations dated July 27, 2004. Our comments on your response are provided below.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational devices, as published in Title 21, Code of Federal Regulations (CFR), Parts 812 and 50 (available at http://www.access.gpo.gov/nara/cfr/index.html. )

The applicable provisions of the CFR are cited for each violation listed below. Some of the violations were not cited on the Form FDA 483, but were evident from the documents that the FDA investigator collected during the inspection.

1. **You failed to ensure that informed consent is obtained in accordance with the provisions of 21 CFR Part 50. [ 21 CFR § 812.100 ].**

   A. You failed to obtain informed consent from 88 of 201 subjects enrolled in Study 3. You are responsible for obtaining informed consent from all subjects prior to their participation in the study to protect the rights, safety, and welfare of subjects under your care.

   In your letter you acknowledged the deficiency and stated that you notified the [redacted] and the University of Maryland at Baltimore IRB that approved the studies regarding this violation. You also promised to monitor all external sites more closely for full compliance through site visits in all future trials. If you are currently conducting or monitoring any trials, we expect that with your response to this letter you will provide documentation of the procedures that you have put in place to ensure that informed consent is obtained in all studies for which you are responsible. If you have currently arranged to conduct trials that have not yet begun, we expect you to send us similar documentation for them. Although we intend to review those procedures, we remind you that you have the ultimate responsibility for ensuring that those procedures are implemented and are adequate to ensure that informed consent is obtained properly for each subject.

   B. Fifty-six of 113 subjects enrolled in Study 3 did not date their signature on the consent forms. Without a dated signature, it is impossible to determine whether the written informed consent was obtained prior to the study procedure.

   You acknowledged this violation in your letter and proposed to perform better monitoring in the future. As we state in 1.A above, we expect that in your response to this letter you will include documentation on procedures

you have implemented in any on-going trials, or that you will implement in any currently-planned future trials, to ensure that this violation does not recur.

2. **You failed to include all basic elements of the informed consent. [ 21 CFR § 50.25(a)(5) ].**

You failed to include one of the basic elements in the informed consent form used for all three studies. The consent forms approved by the University of Maryland at Baltimore IRB and the [redacted] and signed by subjects did not indicate the possibility that FDA might inspect the records.

You acknowledged this violation in your letter, and agreed to include the statement of FDA inspecting subjects' records in the consent forms to be used in future studies and to notify the IRBs regarding this regulatory requirement. As for 1.A and 1.B above, we expect that with your response to this letter you will send us copies of consent forms that you are using in any on-going trials, and copies of consent forms for any trials that you have currently arranged but have not yet begun.

3. **You failed to ensure that the investigation was conducted according to the investigational plan and the signed agreement, and you failed to maintain accurate, complete and current records relating to the receipt, use, and disposition of devices. [ 21 CFR §§ 812.100 and 812.140(a)(2) ].**

The protocols for Studies 1, 2, and 3 require the investigator to maintain an inventory record of devices received and used to assure the sponsor that the materials "will not be used for any purpose other than what is stated in this protocol.... These records must include all dates, lot numbers, quantities received, quantities used, and identification of subject" and account for any devices lost or wasted. You failed to maintain adequate and accurate records regarding the device receipt, disposition, and destruction as shown in the following examples.

A. The protocol for Study 1 states that "[u]pon completion or termination of the study, all unused devices/reagents are to be returned to [redacted] in the original containers to the attention of the study monitor." Study 1 was completed in November, 2003. During the FDA investigation in July, 2004, the FDA investigator discovered that 17 devices (13 from lot [redacted] 4 from lot [redacted] were not returned. Only after the FDA investigator pointed out that fact did someone request instructions from the sponsor about how to handle those devices.

B. As shown in the following table, you did not maintain adequate device reconciliation records. The device accountability was not adequately reconciled between the device receipt log and the inventory log.

| Study / # of subjects enrolled | Device lot # | Number of devices received (Receipt log) | Number of devices used/discarded (Inventory log) | Device discrepancy Excess/unaccounted for |
|---|---|---|---|---|
| Study 3 202 subjects | [redacted] | 250 | 255 | The source of 5 extra devices is not documented |
| Study 3 | [redacted] | 150 | 156 | The source of 6 extra devices is not documented |
| Study 3 | [redacted] | 150 | 139 | Disposal of 11 devices unaccounted for |
| Study 3 | [redacted] | 150 | 118 | Disposal of 32 devices unaccounted for |

You did not maintain records for the disposal of 11 and 32 devices left at the completion of Study 3 for the lot numbers [redacted] and [redacted] respectively, indicating their return to the sponsor. During the inspection, a study team member provided an undated document stating that all remaining devices were discarded at the site in the biohazard trash. The document does not indicate when and how many of the devices were discarded.

B. During the inspection, a study team member corrected the data entries for the receipt, use, and disposition of devices one year after the completion of Study 1.

C. Inventory records for lot [redacted] do not account for two devices used in Study 1. The record on 3/27/03 indicates the number of devices in storage as 277 and the record for the following inventory date, 4/1/03, indicates the number as 275.

In addition, please explain why the informed consent form for Study 3 that was approved by the [redacted] on 3/21/03 bears the pre-printed date of 4/23/03 in the title.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational devices. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies. Your response should include any documentation necessary to show that correction has been achieved.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include injunction and initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational devices.

Please send your written response to:

Ms. Bhanu Kannan
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Lee Bowers, District Director
Food and Drug Administration
6600 Metro Drive, Suite 101
Baltimore, Maryland 21215

[redacted]